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[Title of the Invention] Peroral Anti-Inflammatory Agent

[Abstract]
[Purpose] With oral anti-inflammatory agent of the present invention of which active ingredient is hyaluronic acid, treatment of mucosa at the time of inflammation of oral mucosa or pharyngeal, laryngeal mucosa is performed. Acidic mucopolysaccharides which are inflammation healing substance are exudation-inhibited or turned into low molecules by expectorants and lose healing effect. The present invention supplements healing effect by means of the taken hyaluronic acid and repairs inflammatory mucosa.

[Structure] The oral anti-inflammatory agent of the present invention of which active ingredient is hyaluronic acid was made into aqueous solution, a jellylike state, a candy-like form, or a capsule type of hyaluronic acid. The more macromolecular aqueous solution of sodium hyaluronate is, the better protection and healing effect it has, and the better adhesive effect it has.

[Claims]

[Claim 1] Oral anti-inflammatory agent of which active ingredient is hyaluronic acid.

[Claim 2] Oral anti-inflammatory agent of which active ingredient is hyaluronic acid and which has been made into a jellylike dosage form.

[Claim 3] Oral anti-inflammatory agent of which active ingredient is hyaluronic acid and which has been made into a candy-like dosage form.

[Claim 4] Oral anti-inflammatory agent of which active ingredient is hyaluronic acid and which has been made into an aqueous dosage form.

[Claim 5] Oral anti-inflammatory agent of which active ingredient is hyaluronic acid and which has been made into encapsulated formulation enclosed in a capsule.

[Detailed Description of the Invention]

[0001]

[Field of the Invention] The peroral anti-inflammatory agent of the present invention relates to medical treatment for treatment of oral mucosa or pharyngeal and laryngeal mucosa.

[0002]

[Explanation of Prior Art] Hyaluronic acid widely exists among tissues and body fluids, etc., of vertebrate. Particularly in human beings, it is seen with high concentration inside the umbilical cord, synovial fluid, vitreous body. As local applications of hyaluronic acid, presently, there are an ophthalmic surgery adjunct, eye drops,

a therapeutic agent for osteoarthritis.

[0003] It is said that, as medical actions, hyaluronic acid has inhibition of functions of polymorphonuclear leukocytes, contact inhibition of lymphocytes and target cells, inhibition of macrophages' migration and poor eating*, neovascularization activity of low-molecular hyaluronic acid, radical scavenger effect, effect upon cell proliferation. However, it can also be considered that hyaluronic acid itself does not have bioactivity, and physical properties are incentive substance† of these bioactivity. That is, because it can be considered, for example, hyaluronic acid becomes paratenesis of wound healing substance or inflammatory substance and is deeply involved in the wound healing process and the process of inflammation.

[0004] It is classified in Japan as a drug without drug efficacy on account of being an aqueous injectable agent, and in the U.S. as medical equipment. Physical properties of 1% hyaluronic acid aqueous solution which has been used conventionally are excellent in viscosity and elasticity, and it is generally referred to as viscoelastic substance.

[0005]

[Problem to be Solved by the Invention] To inflammation of mucosa from the upper airway or the upper esophagus up to the mouth at the time of tonsilli-, pharyngi-, laryngitis and airway diseases, anti-inflammatory agents or expectorants are administered. In saliva and phlegm at this time, hyaluronic acid exists.

[0006] However, there are cases where exudation of hyaluronic acid is impeded by exudation inhibition of inflammation healing substance

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* Translator's note: While the word "*hinshoku*" (貧食) in the original Japanese text was translated here verbatim as "poor eating," it may be a typographical error for "*donshoku*" (貪食) which means "phagocytosis."

† Translator's note: While the word "*yuin busshitsu*" (誘因物質) in the original Japanese text was translated here verbatim as "incentive substance," it may be a typographical error for its homophone "*yuin busshitsu*" (誘引物質) which means "attractant."

by administration of anti-inflammatory agents or expectorants. While bromhexine hydrochloride or methylcysteine or the like is prescribed as expectorants for bronchitis, upper respiratory infection, pulmonary tuberculosis, kidney pulmonary disease‡, and postsurgical treatment, for example, it is said that these bromhexine hydrochloride, methylcysteine and the like make phlegm loosen well by increasing secretion which makes phlegm easily loosen up and turning acidic mucopolysaccharides which are one of components of phlegm into low molecules.

[0007]

[Means for Solving the Problem] Therefore, it is to orally administer hyaluronic acid which is one of this [sic] acidic mucopolysaccharides, and to let hyaluronic acid adhere to inflammatory parts of mucosa from the mouth down to the upper airway and heal the parts. In particular, as hyaluronic acid has adhesiveness to inflammatory proteins, the administered hyaluronic acid adheres peculiarly to inflammatory parts. The hyaluronic acid that did not adhere passes through esophagus, a stomach, intestines and is decomposed and absorbed.

[0008] Hyaluronic acid dissolves in water well when made into a base. The hyaluronic acid is easy to be taken when made into an aqueous agent, jelly, a candy, or a saliva-lytic capsule.

[0009] While hyaluronic acid has been known to be wound healing substance, the present invention is characterized in that hyaluronic acid is orally administered and treatment of inflammation of mucosa in tonsilli-, pharyngi-, laryngitis is performed.

[0010]

[Function] It is known that, among connective tissue components in the wound healing process, hyaluronic acid emerges first, at the same time it disappears chondroitin sulfate emerges, and then collagen is

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‡ Translator's note: While the word "*jinpaisho*" (腎肺症) in the original Japanese text was translated here verbatim as "kidney pulmonary disease," it may be a typographical error for its homophone "*jinpaisho*" (塵肺症) which means "pneumoconiosis."

synthesized and becomes cicatrized, and a wound is healed. That is, it is thought that, in the process of repairing tissues after tissue damage due to some cause, for example, inflammation, existence of hyaluronic acid which carries wound healing substance is necessary. Since purified hyaluronic acid has a property to form covalent bonds with proteins, it peculiarly adheres onto mucosa under inflammation wherein inflammatory proteins exist. It is known that sodium hyaluronate has strong water-holding capacity and produces the hydration volume approximately 1,000 times the dry matter volume. When holding water, it has viscoelastic properties of non-Newton flow and has a role of tissue protection and a lubricant. In the present invention, all of these functions are applied, and it is taken for treatment of oral mucosa and laryngeal mucosa.

[0011]

[Embodiment 1] By dissolving sodium hyaluronate 10 mg in distilled water 1 ml together with sodium chloride 90 mg, aqueous solution of sodium hyaluronate was prepared. For sodium hyaluronate, the one of which average molecular weight was 900,000 Dalton approximately and which was extracted and purified from crista galli was used. When the present inventor himself drank for treatment of inflammation of mucosa in laryngitis, he felt tackiness in the inflammatory mucosa since immediately after drinking, coughs stopped the following day, and he was relieved.

[0012]

[Embodiment 2] 3% aqueous solution of sodium hyaluronate of which average molecular weight was 1,200,000 Dalton approximately and which was extracted and purified from crista galli was prepared and made into a jellylike state. It was soaked in absolute alcohol for 24 hours, and the jellylike periphery was further dehydrated and solidified. While it was almost tasteless when this jelly of hyaluronic acid was held in our mouths, it swelled and hydrated slowly and dissolved.

[0013]

[Embodiment 3] 3% aqueous solution of sodium hyaluronate of which

average molecular weight was 1,200,000 Dalton approximately and which was extracted and purified from crista galli was prepared and made into a jellylike plate. It was soaked in absolute alcohol for 24 hours, and the jellylike periphery was further dehydrated and solidified. The solidified hyaluronic acid was made into balls with starch syrup, dried, and made into a candy-like form. It was sweet when this candy of hyaluronic acid was held in our mouths, and it swelled and hydrated slowly and dissolved.

[0014]

[Embodiment 4] 2% aqueous solution of sodium hyaluronate of which average molecular weight was 1,200,000 Dalton approximately and which was extracted and purified from crista galli was prepared and made into a jellylike state. It was made into capsules which dissolve in a mouth.

[0015]

[Effect of the Invention] As explained by the foregoing, with the oral anti-inflammatory agent of the present invention of which main ingredient is hyaluronic acid, treatment of inflammation of mucosa in tonsilli-, pharyngi-, laryngitis can be performed. Since it is considered that this pharmaceutical agent itself does not have pharmacological activity, it hardly has any side effects and is safe. Particularly, when taken in such forms as jelly or candies, it can be taken easily even by the aged or children. Hyaluronic acid is polysaccharides and the substance convertible into throat drops. Since the oral anti-inflammatory agent of the present invention of which main ingredient is hyaluronic acid adheres to inflammatory mucosa, promotes exudation of healing substance and protects the inflammatory mucosa, early recovery of patients can be expected.

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(54) ANTI-INFLAMMATORY AGENT FOR ORAL ADMINISTRATION

(57) Abstract:

PURPOSE: To provide a peroral anti-inflammatory agent containing hyaluronic acid as an active component, having little side effect and high safety and useful for the treatment of inflammation of mucous membrane in amygdalitis, pharyngitis and larynxitis.

CONSTITUTION: Hyaluronic acid is used as an active component. The agent can be prepared in various forms such as jelly, a drop-like aqueous agent or a saliva-soluble capsule. Hyaluronic acid is a kind of acidic mucopolysaccharides and widely present between the tissues and in the body fluid of vertebrate animal. Hyaluronic acid can be bonded to the inflammation part of the mucous membrane from the oral cavity to the upper respiratory tract and cure the inflammation by oral administration of hyaluronic acid. In a connective tissue component in a wound healing stage, hyaluronic acid is developed first and, according to the elimination of the acid, chondroitin sulfate is developed to synthesize a collagen, form cicatrices and heal the wound. Early recovery is possible because of the adhesion of hyaluronic acid to the inflammatory mucous membrane, the promotion of exudation of healing substance and the protection of the inflammatory mucous membrane.

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（書誌＋要約＋請求の範囲）

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(57)【要約】
［目的］ 本発明のヒアルロン酸を有効成分とする経口抗炎症剤で口内粘膜や咽頭、喉頭粘膜炎症時の粘膜の治療を行う。炎症治癒物質である酸性ムコ多糖類が粘膜刺により滲出抑制或いは低分子化され、治癒効果を失う。本発明は服用したヒアルロン酸により治癒効果を補い、炎症粘膜を修復する。
［構成］ 本発明のヒアルロン酸を有効成分とする経口抗炎症剤はヒアルロン酸の水溶剤、ゼリー状、飴玉状、或いはカプセル剤型とした。ヒアルロン酸ナトリウム水溶液は高分子ほど保護・治癒効果があり、炎症粘膜への接着効果がある

【特許請求の範囲】

【請求項１】 ヒアルロン酸を有効成分とする経口抗炎症剤。
【請求項２】 ヒアルロン酸を有効成分とし、ゼリー状の剤型とした経口抗炎症剤。
【請求項３】 ヒアルロン酸を有効成分とし、飴玉状の剤型とした経口抗炎症剤。
【請求項４】 ヒアルロン酸を有効成分とし、水性剤型とした経口抗炎症剤。
【請求項５】 ヒアルロン酸を有効成分とし、カプセルに封入したカプセル剤とした経口抗炎症剤。

詳細な説明

【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明の経口抗炎症剤は口内粘膜や咽・喉頭粘膜治療の為の医療に関する。
【０００２】
【従来技術の説明】ヒアルロン酸は脊椎動物の組織間や体液中等に広く存在している。特に人では、臍帯、関節液、硝子体中に高濃度に見られる。現在、ヒアルロン酸を局所に応用したものとしては、眼科手術補助剤、点眼剤、変形性関節治療剤がある。
【０００３】ヒアルロン酸には薬理作用として、多形核白血球の機能の抑制、リンパ球と標的細胞の接触抑制、マクロファージの遊走及び貪食抑制、低分子ヒアルロン酸の血管新生活性、ラジカルスカベンジャー作用、細胞増殖に対する作用があると言われている。しかしながら、ヒアルロン酸自体には生理活性は無く、物理的性質がこれら生理活性の誘因物質になっているとも考えられる。つまり、例えば、ヒアルロン酸が生理活性物質である創傷治癒物質や炎症性物質の運搬体となり、創傷治癒過程や炎症の過程に深く関与していると考えられるからである。
【０００４】日本では水性注射剤である事より薬効の無い薬剤として、また米国では医療器具として分類されている。 従来より使われている１％ヒアルロン酸水溶液の物理的性質は粘性や弾性に優れており、一般的に粘弾性物質と言われている。
【０００５】
【発明が解決しようとする課題】扁桃、咽頭、喉頭炎及び気道疾患時の気道上部や食道上部より口内までの粘膜
の炎症に対しては抗炎症剤や祛痰剤等が投与されている。この時の唾液、痰中に

はヒアルロン酸が存在する。
【０００６】
しかしながら、抗炎症剤や祛痰剤の投与による炎症治癒物質滲出抑制により、

ヒアルロン酸の滲出が阻害される場合がある。例えば、塩酸ブロムヘキシンや

メチルシステイン等が気管支炎、上気道炎、肺結核、腎肺症や手術後の祛痰剤として処方されるが、これら塩酸ブロムヘキシンやメチルシステイン等は痰が切れやすくなるような分泌物を増加させ、痰の成分の一つである酸性ムコ多糖類を低分子化することにより痰の切れを良くするといわれている。

【０００７】

【課題を解決する為の手段】そこで、この酸性ムコ多糖類の一つであるヒアルロン酸を経口より投与し、口内より気道上部までの粘膜の炎症部位にヒアルロン酸を接着させその部位を治癒させようとするものである。特にヒアルロン酸は炎症性蛋白質と接着性があることより投与したヒアルロン酸は炎症部位に特異的に接着する。接着しなかったヒアルロン酸は食道、胃、腸を通り、分解吸収される。

【０００８】ヒアルロン酸は塩基とすると水によく溶ける。そのヒアルロン酸は水性剤、ゼリー、飴玉、或いは唾液溶解性カプセル剤とすると服用しやすい。

【０００９】ヒアルロン酸は創傷治癒物質と知られているが、本発明はヒアルロン酸を経口投与し、扁桃、咽頭、喉頭炎における粘膜の炎症の治療を行うことを特徴としている。

【００１０】

【作用】創傷治癒過程における結合組織成分ではヒアルロン酸が最初に出現し、それが消失すると共にコンドロイチン硫酸が出現し、そしてコラーゲンが合成され瘢痕化し、傷が治癒することが知られている。つまり何等かの原因で、例えば炎症による、組織障害後の組織の修復過程では創傷治癒物質を運ぶヒアルロン酸が存在することが必要であると考えられている。精製されたヒアルロン酸は蛋白質と共有結合する性質を持っているので炎症性蛋白質の存在する炎症下の粘膜上に特異的に接着する。ヒアルロン酸ナトリウムは保水力が強く、乾燥物容積の約１，０００倍の水和容積となる事が知られている。保水時は非ニュートン流動の粘弾性特性を持っており、組織保護や潤滑剤の役目を持っている。本発明ではこれら全ての作用が応用され、口内粘膜や喉頭粘膜の治療に服用される。

【００１１】

【実施例１】ヒアルロン酸ナトリウム１０ｍｇを塩化ナトリウム９０ｍｇと共に蒸留水１ｍｌに溶解し、ヒアルロン酸ナトリウム水溶液を作成した。ヒアルロン酸ナトリウムは平均分子量約９０万ダルトンで鶏冠より抽出精製したものを使用した。本発明者自ら喉頭炎における粘膜の炎症の治療に飲用したところ、飲用直後より炎症粘膜にべとつき感があり、翌日には咳が止まり、軽快した。

【００１２】

【実施例２】平均分子量約１２０万ダルトンで鶏冠より抽出精製した３％ヒアルロン酸ナトリウム水溶液を作成し、ゼリー状とした。無水アルコールに２４時間浸し、ゼリー状の周囲をより脱水し固くした。このヒアルロン酸のゼリーを口に含んだところ殆ど無味ではあったが、緩徐に膨潤含水し溶解した。

【００１３】

【実施例３】平均分子量約１２０万ダルトンで鶏冠より抽出精製した３％ヒアルロン酸ナトリウム水溶液を作成し、ゼリー状で板状にした。無水アルコールに２４時間浸し、ゼリー状の周囲をより脱水し固くした。固化したヒアルロン酸ナトリウムを水飴と共に丸め、乾燥させ、飴玉状とした。このヒアルロン酸の飴玉を口に含んだところ、甘く、また、緩徐に膨潤含水し溶解した。

【００１４】

【実施例４】平均分子量約１２０万ダルトンで鶏冠より抽出精製した２％ヒアルロン酸ナトリウム水溶液を作成し、ゼリー状とした。これを口内で溶解するカプセル剤とした。

【００１５】

【発明の効果】以上説明したように本発明のヒアルロン酸を主成分とする経口抗炎症剤で扁桃、咽頭、喉頭炎における粘膜の炎症の治療が行える。本薬剤自体は薬理活性が無いと考えられるので副作用は殆ど無く、安全である。特に、ゼリーや飴玉状等にして服用すれば、老人や子供でも簡単に服用される。ヒアルロン酸は多糖類であり、喉飴として転用可能な物質である。本発明のヒアルロン酸を主成分とする経口抗炎症剤は炎症粘膜に接着し、治癒物質の滲出を促し、その炎症粘膜を保護するので患者の早期回復が期待できる。